REMARKS

No amendments are made herein. Claims 1-4, 6-11, and 14-18 are pending. The Examiner has withdrawn Claims 14-18, stating that they were directed to an invention independent or distinct from the invention originally claimed. Applicants retain all rights of rejoinder for Claims 14-18. Applicants have carefully considered the Examiner's rejections, but respectfully submit that the claims are allowable for at least the following reasons.

Rejections under § 112 – Enablement

The Examiner rejected Claims 1-4 and 6-11 under 35 U.S.C. § 112, ¶ 1. The Examiner alleged that the specification does not reasonably provide enablement for muscarinic agonists, with the exception of compounds such as xanomeline, oxotremorine, milameline, formula VII, VIII, and IX of the instant application. In particular, the Examiner contends that undue experimentation would be required where it is not predictable that all muscarinic receptor agonists that selectively activate M(1) type treat neuropathic pain without alleviating acute pain. In addressing the *Wands* factor of Quantity of Experimentation, the Examiner stated that it would require that one of skill in the art to envision formulation, dosage, duration, route, an animal model, and tests that a compound treats neuropathic pain without alleviating acute pain.

Applicants respectfully submit that one skilled in the art could follow the teachings of the instant application to identify and select compounds that selectively activates the M(1) receptor and treat neuropathic pain without alleviating acute pain. The specification describes assays to readily verify that agonists selective for the M(1) receptor can be used to treat neuropathic pain without alleviating acute pain.

Applicants are submitting with this response a Declaration by Douglas W. Bonhaus, Ph.D. This Declaration demonstrates that the invention as claimed and disclosed is operable and can be made and used without undue experimentation by following the teachings of the specification. For example, the Declaration discloses four additional selective M(1) receptor agonists, labeled Compounds 1-4, that were readily verified as effective at treating neuropathic pain without alleviating acute pain by using the teachings of the instant application. To maintain the confidential proprietary nature of Compounds 1-4, the structures of Compounds 1-4 are not

disclosed in the Declaration or herein. Compounds 1-4 are all structurally similar to compounds of formula VII, VIII, and IX, although three of them do not fall within the scope of the generic structures presented in Claims 14-18.

The Declaration demonstrates that assays similar to the R-SAT assay described in Example 1 of the specification can readily identify compounds that are selective for the M(1) receptor without undue experimentation by one skilled in the art. Another assay, a sciatic nerve lesion assay similar to the assay described in Example 3 of the instant application, can readily verify that such selective compounds for the M(1) receptor are useful to treat neuropathic pain, also without undue experimentation. A similar assay using transgenic mice lacking the M(1) receptor can also be used to test whether the anti-neuropathic pain properties of the compounds are due to action through the M(1) receptor. The Declaration also demonstrates that a tail flick assay, similar to the assay described in the instant application under the heading 'Acute Thermal Analgesia' of Example 1, can readily verify that selective M(1) agonists alleviate neuropathic pain without alleviating acute pain.

In sum, the Declaration demonstrates that the instant application provides one skilled in the art with all assays required to identify and select compounds that are selective for the M(1) receptor and can be used to treat neuropathic pain without alleviating acute pain without undue experimentation. The results further support that selective M(1) agonism is predictive for efficacy against neuropathic pain while not alleviating acute pain. Accordingly, the Applicants respectfully submit that Claim 1-4 and 6-11 are enabled.

Rejections under § 103

The Examiner rejected Claims 1-4 and 6-11 under 35 U.S.C. § 103(a) over Lavand'homme *et al.* (Anesthesiology, 1999, 91, 1455-61), Andersson *et al.* I (WO 01/83472) and in further view of Mitchell (J. of Pain and Symptom Management, Vol. 21, 5, May 2001). Lavand'homme discloses that the muscarinic agonist bethanechol is effective against allodynia. Andersson *et al.* I discloses the compound of formula VII as a muscarinic agonist and teaches that it can be used to treat "pain." Mitchell discloses that neuropathic pain symptoms can include allodynia and hyperalgesia.

The Examiner similarly rejected Claims 1-4 and 6-11 under 35 U.S.C. § 103(a) over Lavand'homme *et al.* (Anesthesiology, 1999, 91, 1455-61), Andersson *et al.* II (US 2002/0037886) and in further view of Mitchell (J. of Pain and Symptom Management, Vol. 21, 5, May 2001). Andersson *et al.* II also discloses the compound of formula VII as a muscarinic agonist

As an initial matter, Applicants respectfully submit that none the cited art render obvious Claims 1-4 and 6-11. None of the cited art teach or suggest all limitations of the pending claims. Claim 1 recites treating neuropathic pain without alleviating acute pain using a selective M(1) activator. Similarly, Claim 7 recites identifying a compound that alleviates hyperalgesia or allodynia without alleviating acute pain by using a selective muscarinic receptor test compound. As the Examiner recognized in the Office Action dated June 19, 2007, Lavand'homme and Mitchell do not disclose that compounds having activity at muscarinic receptors, such as the compound of formula VII, can be used to treat neuropathic pain without alleviating acute pain. Similarly, neither Andersson *et al.* I nor II disclose that compounds having activity at muscarinic receptors, such as the compound of formula VII, can be used to treat neuropathic pain without alleviating acute pain. Thus, none of the cited art teach or suggest all limitations of the pending claims.

Additionally, Applicants' discovery of muscarinic agonists that alleviate neuropathic pain without alleviating acute pain is an unexpected result. Absence of a property which a claimed invention would have been expected to possess based on the teachings of the prior art is evidence of unobviousness. MPEP 716.02(a) IV. *See, Ex parte Mead Johnson & Co.* 227 USPQ 78 (Bd. Pat. App. & Inter. 1985) (Based on prior art disclosures, claimed compounds would have been expected to possess beta-andrenergic blocking activity; the fact that claimed compounds did not possess such activity was an unexpected result sufficient to establish unobviousness within the meaning of 35 U.S.C. 103). The cited art collectively disclose that muscarinic agonists are effective to treat pain. Nothing in the art suggests that particular pain states could be selectively treated over other pain states. From this cited art it would be expected that muscarinic agonists could be used to treat all types of pain (i.e., both neuropathic and acute pain).

However, Applicants have surprisingly discovered that selective M(1) agonists alleviate neuropathic pain without disrupting normal nociception. In other words, these compounds can

be used to treat pathological pain states (pain when there should not be pain), but do not impair the ability to perceive normal painful stimulus, such as when a hand is placed on a hot stove. Thus, Applicants have discovered a class of compounds that can be used to treat chronic neuropathic pain without disrupting the ability to perceive normal painful stimulus – a vital protective mechanism. In other words, Applicants have discovered selective muscarinic agonists that differentiate between different types of "pain" and can alleviate neuropathic pain without alleviating acute pain. Accordingly, Claims 1-4 and 6-11 provide unexpected results and are not obvious.

In addition, Applicants respectfully submit that one skilled in the art would not be motivated to use the compounds of Andersson *et al.* I and II for the indication taught by Lavand'homme. Lavand'homme discloses bethanechol as effective in reducing allodynia. However, bethanechol was known to exert its effects through muscarinic receptor subtypes other than the M(1) subtype. *See,* De Vos W.C, Am. J. Physiol. (1993) 265:G628-637; Mazza E. *et al*, Eur. J. Pharmacol. (1994) 254: 17-20, attached as Exhibit A. One skilled in the art would not be motivated to use muscarinic agonists selective for the M(1) subtype for an indication that is taught as being treatable with a compound selective for other muscarinic subtypes. As such, Applicants respectfully submit that it would not be obvious to use the compound of formula VII for the indication taught in Lavand'homme.

For all the reasons above, the Applicants respectfully submit that Claims 1-4 and 6-11 are not obvious.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history

shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: August 21, '08

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